

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 8, ISSUE 4 ■ JULY-AUGUST 2000

DIRECTORY ATTRACTS CRITICAL MASS TO MAKE A DAY OF IT

The Hispanic Scientists Directory currently contains the names and biographical data of about 70 scientists at NIH and FDA—surely not the actual number of people of Hispanic origin that populate NIH and FDA labs, but a sufficient and growing number of self-subscribed individuals to build Hispanic Scientists Day at NIH.

Whether this day will occur every year—and what forms recognition of the research of Hispanic scientists may take—is not certain, said Nancy Vázquez-Maldonado, a prime mover of both the directory and the day, but the professional and personal connections established through the directory are here to stay.

The directory gives each person's phone, fax, and e-mail; institute and lab; job title, degree, and degree-granting institution; dates of arrival and expected departure from NIH or FDA; research areas of interest, and country of origin. Most scientists now listed come from Puerto Rico and the countries of South America, with the remainder representing Mexico, Spain, Central America, Cuba, and the United States. The address is

<<http://helix.nih.gov/felcom/latino2.html>>.

Most scientists who have listed themselves in the directory, Vázquez-Maldonado said, credit it for having enabled them to connect with other Hispanic scientists—to collaborate or just to be able to speak Spanish.

—FP

CON MUCHO GUSTO: HISPANIC SCIENTISTS AT NIH SHOWCASE THEIR RESEARCH

by Cynthia Delgado

In what its wearied but exhilarated organizers hope will be a continuing event at NIH, the first Hispanic Scientists Day (June 5) captured the diversity of research pursuits among NIH scientists who grew up in countries or homes where Spanish was the first or second language.



Fran Pollner

Mission Accomplished (left to right): Nancy Vázquez-Maldonado, FDA, Carmen Collazo-Custodio, NIAID, Carolina Nadel, NCBI, and OIR Assistant Director Arlyn García-Pérez, NHLBI, await the start of the day they worked months to put together.



Fran Pollner

Juan Rivera (left), NIAMS, delivered the keynote lecture at the NIH Hispanic Scientists Day. Ray Mejia, president of the NIH Hispanic Employee Organization, announced two symposia on Health Disparities in Minority Populations September 15 and October 4.

institutes across campus joined in a poster display following a keynote lecture by Juan Rivera, senior investigator and head of the Signal Transduction Group (see *The NIH Catalyst*, January–February 2000, page 13), NIAMS. Rivera's NIH career started when he was a first-year college student and included working as a lab tech here while he was getting advanced degrees in immunology. His talk on Fc receptor signaling was further elaborated in one of the posters of the day, presented by Jesus Buonomo, a postbac student in his lab (see page 5).

Following is a small sample of the research presented that day.

Alonzo García, postdoc, Laboratory of Viral Diseases, NIAID: Identification and characterization of bacterial-type DNA Holliday junction resolvase in poxviruses



Cynthia Delgado

Alonzo García

In 1964, Holliday proposed a model of homologous DNA recombination to explain the sequence of molecular events that occur between two chromosomes involved in genetic exchange. A structural intermediate of the model, and a catalytic "hot spot," was dubbed a Holliday junction (HJ). Since that time, the key molecular components of homologous recombination have been dissected in *Escherichia coli*. The dimeric endonuclease RuvC is one such component that resolves the HJ into duplex products by symmetrically nicking two of the four DNA strands. García and his colleagues at NIAID and the NLM's National Center for Biotechnology Information are the first to identify a bacteria-like HJ resolvase in viruses that infect eukaryotic cells. He notes that "until now it had only been found in bacteriophages, bacteria, and yeast." His team is now exploring what role the enzyme plays in virus infection.

The team reported that with the aid of "protein alignment and threading programs, [they] identified critical structural

CONTENTS

1 Hispanic Scientists Take Center Stage

2 Guest Edit: Title 42

3 FAES/Women's Health

6–10 INTEREST GROUP DIRECTORY/Cartoon

11–15 Recently Tenured

16 Catalytic Questions

TITLE 42: SNAPPIER RECRUITMENT FOR THE SENIOR RANKS

Because "Title 42" is becoming something of a household word around NIH—and many of our recent senior recruits have arrived under the Title 42 umbrella—it seems fitting to elaborate on some of its features and new uses.

Generally, Title 42 (the shorthand we use to cite a personnel authority under the Public Health Service Act, which appears in Title 42 of the U.S. Code) is a measure that has enhanced NIH's ability to bring scientists into the intramural research program (IRP) and to advance those already here. It now gives NIH greater flexibility to appoint and pay senior scientists and has simplified the personnel process. The authority was first put into law more than 30 years ago and may also be applied to visiting intramural scientists and some extramural staff, but those uses will not be addressed in this column. A recent interpretation by the HHS General Counsel's Office now lets us use this legal authority to appoint and pay scientists at all levels, including our senior ranks.

What does Title 42 authority mean for the IRP and why is it beneficial?

NIH can now use the authority for scientists appointed as staff scientists and clinicians, for tenure-track investigators, and, when it is the best option, for tenured senior investigators. Once the usual competitive search has been completed, we can appoint the scientist without further administrative red tape. Thus, Title 42 saves time and allows the hiring lab to snap up the very best researchers and make a formal offer much more quickly—a process that fits the scientific environment better.

Another advantage of Title 42 is that its pay structure is much more flexible than other systems. Unlike the "lock-step" system of the General Schedule (GS), Title 42 allows us to set pay at the appropriate level, based on the individual's scientific expertise and competitive market rates.

What are the relationships between Title 42, permanence, and tenure?

Intramural tenure at NIH denotes independent scientific resources and salary that are continued throughout a scientist's productive career. The decision to grant tenure at NIH is independent of hiring authority. Title 42 appointments must be renewed every 1 to 5 years, whereas most GS appointments do not require renewal. Title 42 positions may seem somewhat tenuous, but this is largely a matter of appearance. Many of the scientists appointed under Title 42—such as scientists in the Senior Biomedical Research Service—are leading lights in the intramural program and we expect they will spend their entire career at NIH.

How are Title 42 salaries set? What criteria are used to set pay?

First and foremost, the individual's scientific credentials must be peer-reviewed to ensure that she

or he meets the requirements for the position. This is done in one of several ways. For outside recruits, the search committee reviews the accomplishments of all applicants and recommends a group of finalists to the selecting official. A number of institutes and centers (ICs) ask their promotion review boards to provide input on these recommendations. At higher salary levels, if Title 42 is applied to a current NIH scientist, the deputy director for intramural research (DDIR) asks at least two senior scientists with knowledge of the area to review the nominee. Their recommendations will be weighed along with a recent Board of Scientific Counselors review.

Once the credentials review is completed, the next step is to set salary. The scientific director and the institute director make salary recommendations for scientists in their ICs. The ICs may approve pay up to Executive Level 1—the salary of the HHS secretary and the NIH director—currently \$157,000.

When the proposed salary is higher than Executive Level 1, or where a proposed increase is greater than \$30,000, a board chaired by the DDIR and the deputy director for management also looks at pay. For clinical scientists, this board includes the director of the Clinical Center, several clinical directors, and the director of human resources.

Thanks to the pay flexibility of Title 42, salary decisions may take into account pay levels for comparable senior positions in universities and other private research environments. Considerations may also include the current salary of individuals recruited from outside and competing offers.

The board also considers pay equity within NIH—what scientists with similar experience, accomplishments, and duties are making. After these deliberations, most cases proceed to the NIH director for final approval; in rare instances, we must obtain approval from the office of the HHS secretary.

What is likely in the future with Title 42?

I foresee several things. First, there is growing interest in more guidelines for setting competitive salaries. What shape such guidelines would take is not clear yet, but a set of overlapping salary bands for different professional designations may evolve.

Pay equity among scientists is another very important issue—the more flexible the system, the greater the chance of imbalances. We will have to remain vigilant to ensure that salaries across institutes and centers are based on scientific accomplishments, responsibilities, and experience.

Finally, we need to ensure that our Title 42 authority is not compromised by inappropriate uses. We want to be sure that our pay structure can pass muster internally and during any outside independent review. To safeguard this mechanism that has helped us attract, recruit, and retain many outstanding scientists, we will continue careful oversight of Title 42 at NIH.

—Stephen Benowitz

NIH Director of Human Resources

FAES: NEW TERM, (RELATIVELY) NEW DEAN, NEW COURSES, AND A SEARCH FOR NEW TEACHERS AMONG NIH FELLOWS

The FAES (Foundation for Advanced Education in Science) Graduate School at NIH launches its fall semester the week of September 18. The deadline for mail-in registration is **August 31**. On-site registration will be held from **September 6 through 12**. (The fall catalogue is online at the FAES web site: <http://www.faes.org>).

Each year, about 3,000 individuals from NIH and the surrounding community participate in the school's nearly 200 continuing education courses. The faculty is made up primarily of NIH permanent scientific staff, but FAES has a new dean who would like to expand the presence of NIH fellows at the school—not only as students but, more significantly, as teachers.

Constance Tom Noguchi, chief of the Molecular Cell Biology Section in the Laboratory of Chemical Biology, NIDDK, stepped in as FAES dean at the end of the Fall 1999 semester. Her predecessor, Paul Torrence, had worked with the NIH Fellows Committee (FELCOM; see page 10) to create an online database, accessible via the FAES web site, of postdoctoral fellows qualified to teach specific topics in biomedical research, a resource that FAES faculty and others could plumb for guest lecturers.

The next step, Noguchi says, is for more fellows to organize their own courses—an activity she helped foment by issuing a general call to NIH Interest Groups (see Directory, starting on page 6) for new courses. Among those taking up the challenge is Carol Torgan, a senior staff fellow in NHLBI, who, together with Christine Winters of NINDS, is offering a new course (Biology 431) that explores recent advances and controversies in skeletal and cardiac muscle.

Subject areas missing from the FAES curriculum or expandable, in Noguchi's view, include such timely topics as genomics and bioinformatics, as well as more classical subjects such as developmental biology. At the moment,



Fran Pollner

Connie Noguchi

Women's Health Research Comes of FAES Age

One of the FAES newcomers is called "Women's Health: A Clinical Research Update"—a course, say its coordinators, whose time has come as surely as the rush to close the chasms in women's health research that surfaced a decade ago.

Emerging on the 10th anniversary this fall of the NIH Office of Research on Women's Health (to be celebrated September 10 and 11), the course will cover such areas as immunity and autoimmune diseases, endocrinology, cardiovascular health, bone and musculoskeletal disorders, cancer, digestive disorders, infectious diseases, behavioral and social sciences, neuroscience, and reproductive health. These issues will be addressed in the context of developmental stages—from infancy and childhood through adolescence, reproductive and middle years, and old age. Due consideration will be paid to the effects of racial, ethnic, and cultural diversity.

Meant to foster communication among biomedical and behavioral scientists in fields related to women's health, the course is coordinated by Carmen Pastor, adjunct scientist, and Lawrence Nelson, senior clinical investigator, Gynecologic Endocrinology Unit, Section on Women's Health Research, NICHD, with input from a planning committee headed by Vivian Pinn, NIH associate director for research on women's health.

"Women's Health: A Clinical Research Update," will be held Thursday evenings, starting September 21, from 5:30 to 7:30 p.m. and will extend over the fall and spring semesters, for two credits each. It will be offered in alternate years. Prerequisites are graduate level training or experience in the biomedical or health sciences or consent of the coordinators. For more information, contact Carmen Pastor or Larry Nelson:

<pastorca@mail.nih.gov> or <nelsonl@cc1.nichd.nih.gov>.

Ye Olde Bookshoppe

For about 25 years of the more than 40 years FAES has existed, the FAES bookstore has been the place on campus to buy the books required for the courses. But the bookstore goes beyond the required FAES texts, offering a comprehensive array of biomedical and other scientific books, including books related to the teleconferencing classes sponsored by the Office of Education and off-campus universities. Some materials are available in CD form. And some titles have little to do with scientific courses—like travel guides, cookbooks, some best sellers, and children's books. Browsing, says store manager Jerryann Gilbert, is welcomed. The bookstore special orders titles, reserves books, and handles shipments within the United States. Government credit cards and institute purchase orders can be used, and FAES members get a 5 percent discount on all purchases.

The bookstore is located on the B1 level of building 10, room L101, opposite the cafeteria and bank and adjacent to and a bit behind the gift shop. It's open Monday through Friday, 8:30 am to 4:00 pm. Its web address is www.faes.org/bookstor.htm.

there are only two course offerings in bioinformatics, which—based on the overflow that greeted the new Introduction to Bioinformatics course offered last spring—may not be nearly enough.

A perusal of the new 2000-2001 catalog shows 17 new science and medicine courses, including topics in neurophysiology and development, stem cells, clinical carcinogenesis, women's health,

biomedical ethics, impacts of biotechnology, and clinical preventive medicine. And as testimony to the eclectic nature of the FAES learning environment, there are also new courses in such subjects as French and darkroom techniques.

For more information about the FAES graduate school and the fall session, call Audrey Lyons at 301-496-7976; e-mail:

<lyonsa@mail.nih.gov>.

Research Festival Poster Deadline

The NIH Research Festival—the annual showcase of the Intramural Research Program—is scheduled for October 10 through 13. The deadline for **online poster registration is 5:00 p.m., Monday, August 7**. Applicants will be notified of acceptance by August 21. The festival organizing committee, co-chaired this year by NHLBI scientific directors Robert Balaban and Elizabeth Nabel, requests a limit of one poster submission per first author. Plenary sessions feature nitric oxide, angiogenesis, and genome analysis. A schedule of events and online poster registration can be found at

<<http://festival2000.nih.gov>>.

HISPANIC SCIENTISTS

continued from page 1

elements of RuvC . . . in uncharacterized open reading frames from all poxviruses and an iridovirus." The group noted that the gene product of the Vaccinia virus gene A22R had sequence and structural similarities to the RuvC bacterial resolvase.

Further, they found that the recombinant protein rA22 specifically bound to and cleaved a synthetic HJ, yielding duplex molecules. This catalytic activity was not present against single- or double-stranded DNA, Y-junctions, or duplex-branched molecules. Although mutations in conserved amino acids in rA22 required for endonuclease activity abrogated catalytic activity, specific binding to the HJ was not inhibited. They postulated that the HJ resolvase plays a role during Vaccinia virus infection through its effects on viral DNA processing and resolution of recombinant DNA intermediates. This theory was supported by the absence of resolution when they co-transfected a mutated A22R and a cruciform-structure-containing plasmid (which has a "Holliday-like" junction) in cells infected with wild-type virus.

Carmen M. Collazo-Custodio, postdoc, Laboratory of Parasitic Diseases, NIAID:

The IFN- γ -inducible GTPase (IGTP) is required for in vivo control of *Toxoplasma gondii* infection in both hematopoietic and nonhematopoietic host cells

Toxoplasma gondii is an intracellular protozoan parasite and the etiologic agent responsible for toxoplasmosis. The early acute phase of infection is characterized by rapid replication in a variety of nucleated host cells. A potent cell-mediated immune response by the host is thought to result in a shift to the chronic phase in which slow-growing forms called bradyzoites are contained within tissue cysts. These cysts convey protective immunity but can also be the source of reactivated infection. Although the precise mechanisms are not fully understood, numerous studies have shown the importance of interferon- γ (IFN- γ) in both acute and chronic phases of *T. gondii* infection.

Collazo-Custodio and her NIAID colleagues, in collaboration with Gregory Taylor, a former NCI postdoc now at Duke University Medical Center in Durham, N.C., studied mice that lacked the IFN- γ -inducible GTPase (IGTP) to determine the nature of its role in the intracellular control of *T. gondii*. They found that IGTP-deficient mice exhibited a complete loss of

host resistance to infection, as well as the inability to clear the parasites from host tissues. These animals did, however, retain normal IL-12, IFN- γ , and nitric oxide levels associated with essential mechanisms of the immune response.

Reciprocal bone marrow chimeras between knockout and wild-type mice revealed the tissue compartments in which IGTP functions in host resistance. In the control group, wild-type mice reconstituted with wild-type bone marrow were resistant to *T. gondii* infection and displayed long-term survival. But wild-type mice reconstituted with knockout bone marrow and knockout mice reconstituted with either wild-type or knockout bone marrow exhibited similar profiles when infected, dying within 9 to 11 days of exposure. These observations, the team reported, indicate that "IGTP is required for control of *T. gondii* infection by both hematopoietic and nonhematopoietic cells and . . . is likely to be involved in the common intracellular pathway used by these two lineages to limit tachyzoite growth."

The group has now shifted its focus to the chronic phase of infection and to localization studies of IGTP in normal vs. infected cells.

Maria Ruiz-Hidalgo, Fogarty fellow, Laboratory of Immunobiology, CBER, FDA:

Notch-1 is required for adipogenesis of 3T3-L1 cells and affects the way these cells interpret the Ras signal

The Notch family of genes encodes transmembrane receptors, which are responsible for intracellular signals that affect cell fate during differentiation. Numerous reports have demonstrated that in some systems Notch expression is a characteristic of the undifferentiated state of many cell types during development. Ruiz-Hidalgo and her colleagues have found the contrary in their system.

Examining adipogenesis of 3T3-L1 cells, a well-characterized system of differentiation, the team showed that Notch-1 acted as an accessory to differentiate the cells. When Notch-1 signaling was blocked by ligand interference or transfection with constructs encompassing Notch-1 cDNA

in antisense orientation, the cells remained in an undifferentiated state despite hormone induction. To explain this phenomenon, the team explored downstream events in the differentiation pathway, specifically, the expression of transcription factors of the helix-loop-helix family, such as PPAR δ and PPAR γ . They found that when Notch-1 ex-

pression was decreased, so was the expression of these transcription factors. "PPAR γ is especially important," says Ruiz-Hidalgo, "and PPAR γ expression is decreased when Notch-1 is not in the cells."

Their recent investigations suggest that the levels of expression of Notch-1 are important for the interpretation of extracellular signals. In opposition to previous reports indicating that constitutively active Ras induces adipogenesis of 3T3-L1 in the absence of inductors, they observed that activated Ras expression induced transformation and no differentiation in control 3T3-L1 cells and in cells with low Notch-1 expression. Interestingly, properties associated with oncogenic transformation were inversely proportional to the level of Notch-1 expression in these cells. This effect appeared to be mediated, at least in part, through a different pattern of activation of MAP kinase.

"With *much* more work," Ruiz-Hidalgo says, light could possibly be shed on new strategies to block malignant transformation or control the differentiation of cells grown for transplantation and cell therapy.

Carolina Nadel, postdoc, NCBI, NLM: Genes and disease—a web site of short descriptions of inherited disorders

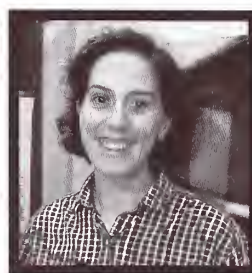
Nadel is a member of the team that provides ongoing update of the NCBI "Genes and Disease" web site,

<<http://www.ncbi.nlm.nih.gov/disease/>>,

a collection of short reports on human genetic diseases. Although the site was established to disseminate information to the general public, it's useful for physicians as well, she says. Each disease page

includes a clinical synopsis, followed by the condition's genetic underpinnings and, when applicable, information about the involved protein(s). The last paragraph, Nadel says, "usually looks to the future" and may describe mouse models, diagnostic factors, and treatment options.

Among the links that connect users to pertinent databases are OMIM,



Cynthia Delgado

Maria Ruiz-Hidalgo



Cynthia Delgado

Carmen Collazo-Custodio



Cynthia Delgado

Carolina Nadel

<<http://www.ncbi.nlm.nih.gov:80/Omim/>>, a comprehensive gene mapping site; LocusLink,

<<http://www.ncbi.nlm.nih.gov/LocusLink/>>,

for gene and loci information; and Entrez, <<http://www.ncbi.nlm.nih.gov/Entrez/>>, a nucleotide and protein sequence databank integration site. The group plans to connect the site to the completed map of the human genome in the coming months. A link to the literature database PubMed,

<<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db-PubMed>>,

is "set up so that the key papers, usually two to three," will be listed, Nadel says. The relevant publications in the last six months are also presented upon a click on "recent literature." At the bottom of the page are "more links to support groups and information for patients and families."

The site now includes between 60 and 70 diseases organized by categories (for example, "cancer," "metabolism," "immune system"). The team is in the midst of reorganizing the information, however, to emphasize the disease itself rather than the molecular nature of its etiology.

Yesenia Rivera, pre-IRTA cancer research trainee, Tumor Cell Biology Section, Medicine Branch, NCI: Geldanamycin, an Hsp90 antagonist, blocks both NF κ B and AKT-dependent survival pathways in tumor cells

Rivera cites the wording in her group's abstract to explain the rationale of their research: "Several anticancer drugs, including Adriamycin, have been shown to induce survival pathways in cancer cells, thus counteracting their own cytotoxicity. The transcription factor NF κ B and kinase AKT mediate two of the survival pathways." She and her teammates are examining ways to block these pathways.

The group's latest data demonstrate that geldanamycin (GA) can augment the cytotoxic effects of Adriamycin. GA is an antagonist to the chaperone protein Hsp90, which imbues stability and function to kinases involved in both pathways. GA exerts its effects by removing apoptotic blocks induced by Adriamycin along both pathways. For example, GA inhibited Adriamycin-induced NF κ B activation, possibly by destabilizing IKK kinases (IKK α and IKK β), thereby blocking NF κ B accumulation in the nucleus and promoting induction of apoptosis. Similarly, they found that GA destabilizes AKT, thus preventing the phosphorylation of an apoptotic tran-

scription factor, FKHL1, resulting in its nuclear accumulation and the triggering of apoptosis.

The combination of Adriamycin and GA scored higher than either alone in assays for toxicity and apoptotic activity. A Phase I clinical trial of a GA derivative in the treatment of solid tumors is underway, and a Phase II trial of a combination GA-Adriamycin arm is being considered.

Nancy Vázquez-Maldonado, postdoc, Division of Therapeutic Proteins, CBER, FDA:

IL-4 suppresses IFN- γ -induced Fc γ RI (CD64) gene expression in human monocytes by inhibiting STAT1 activation

The IFN- γ signal transduction pathway is initiated by a specific ligand-receptor interaction that triggers a series of phosphorylating and signaling events that culminate in transcription stimulation of genes such as , that influence the final phenotype of activated macrophages, such as *Fc γ RI*, *ICAM-1*, and *B7*.

IL-4 is a cytokine known to inhibit several IFN- γ -inducible genes in monocytes. Vázquez-Maldonado and FDA colleagues, with collaborators at Virginia Commonwealth University in Richmond, believe they have deciphered one mechanism by which IL-4 mediates this inhibition.

Pretreatment of monocytes with IL-4 significantly reduced both the mRNA levels of *Fc γ RI* and the expression of its protein, CD64. These findings correlated with reduced tyrosine phosphorylation and nuclear translocation of STAT1 (signal transducers and activators of transcription), signal transduction events associated with IFN- γ -inducible gene expression.

Several lines of evidence suggested that de novo protein synthesis was required for the inhibitory effects of IL-4. First, inhibition of STAT1 activity required pretreatment of cells with IL-4 an hour before stimulation with IFN- γ . Second, IL-4 inhibition was abrogated by the addition of actinomycin D, a potent transcription inhibitor, and correlated with increased expression of the *SOCS-1* (suppressors of cytokine signaling) gene.

Further studies in a murine system in-



Cynthia Delgado

Nancy Vázquez-Maldonado

dicated that IL-4 inhibition was dependent upon SOCS-1 protein and STAT6 as well. SOCS-1 is known to prevent transcription initiation by blocking STAT1 activation in the JAK (Janus kinase)/STAT signaling pathway. The team found that "IL-4 induced the expression of SOCS-1 and inhibited activation of STAT1 in

macrophages from wild-type but not STAT6 knockout mice."

These studies, Vázquez-Maldonado says, should further elucidate the counter-regulatory pathways of cytokines in human monocytes and may have implications in the management of chronic inflammatory diseases.

Jesus Buonomo, postbac, Arthritis and Rheumatism Branch, NIAMS: Studies on Vav localization and function

Vav is a proto-oncogene that functions as a guanine nucleotide exchange factor for the Rho family of proteins and is believed to play an essential role in signal transduction of hematopoietic cells. The protein product of the *Vav1* gene exhibits several structural motifs, including a conserved Dbl homology domain and an SH2 domain that interact with kinases, adaptor molecules, and negative regulators of signal transduction. Vav1 becomes associated with the plasma membrane of activated mast cells, in cholesterol-rich lipid rafts upon antigen cross-linking of the high-affinity receptor for IgE (Fc ϵ RI).

Buonomo and his colleagues began their investigation by asking the question: "Is Vav1 localization to the plasma membrane and/or lipid rafts sufficient to activate function?" They looked for answers using co-localization studies with fluorescent or epitope-tagged constructs of Vav1. These constructs included sequences targeting Vav1 either to the plasma membrane (PM) or the lipid raft, as well as mutations in functional domains.

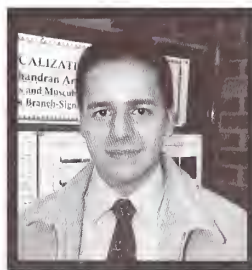
Preliminary results indicated that Vav1 localized to the PM as a micro-aggregate upon Fc ϵ RI stimulation, but was not PM-associated in unstimulated cells. Further, they observed that Fc ϵ RI and Vav1 co-localization was dependent on the SH2 domain of Vav1.

They also discovered that Vav1 co-localized with LAT (linker of the activation of T cells), a protein found in lipid rafts. The group now plans to study the effect of Vav1 localization and function on signaling via the small GTPase Rac1 and c-jun NH₂-terminal kinase (JNK1). ■



Cynthia Delgado

Yesenia Rivera



Cynthia Delgado

Jesus Buonomo

INTERINSTITUTE INTEREST GROUP DIRECTORY

Web Access

Note: Although not all the sites are up to date, nearly all the Interest Groups have web sites that can be accessed through the NIH Home Page (<<http://www.nih.gov/>>) by clicking on "Scientific Resources," then "Special Interest Groups," and then the targeted group(s).

MAJOR INTEREST GROUPS

Cell Biology Interest Group

Meeting time: Once every four months
Meeting place: Building 32, Library
Contact: Jennifer Lippincott-Schwartz
Phone: 402-1010; 402-1009
E-mail: <jlippin@helix.nih.gov>
Listserv: subscribe to CELBIO-L

Clinical Research Interest Group

Meeting time and place: sponsors Clinical Center Grand Rounds once every other month
Contact: Cliff Lane
Phone: 496-7196
E-mail: <clane@nih.gov>

Genetics Interest Group

Meeting time: Usually 2nd Tuesday, 4:00 pm
Meeting place: Building 49, Conference Room A and B
Contact 1: Heinz Arnheiter
Phone: 496-1645
E-mail: <ha3p@nih.gov>
Contact 2: Beverly Mock
Phone: 496-2360
E-mail: <bev@helix.nih.gov>
Listserv: subscribe to GIG-L@list.NIH.GOV

Immunology Interest Group

Meeting time: Each Wednesday (except summer), 4:15 pm
Meeting place: Building 10, Lipsett Auditorium
Contact: William Paul
Phone: 496-5046
E-mail: <wpaul@niaid.nih.gov>
ListServ: subscribe to IMMUNI-L at Listserv@LIST.NIH.GOV

Molecular Biology/Biochemistry Interest Group

Meeting time: Yearly to consider speakers
Meeting place: Building 8, Room 122
Contact: Reed Wickner
Phone: 496-3452
E-mail: <wickner@helix.nih.gov>

Neuroscience Interest Group

Meeting time: alternate Fridays, 4:30 pm
Meeting place: Cloisters, Rathskeller
Contact 1: Chip Gerfen
Phone: 496-4341
E-mail: <gerfen@helix.nih.gov>
Contact 2: Betsy Murray
Phone: 496-5625, X-227
E-mail: <eam@ln.nimh.nih.gov>

Structural Biology Interest Group

Meeting time and place: Announced to members by e-mail and regular mail
Contact 1: Adrian Parsegian
Phone: 496-6561
E-mail: <aparsegi@helix.nih.gov>
Contact 2: Marius Clore
Phone: 496-0782
To register for e-mail announcements:
E-mail <cch@discus.niams.nih.gov>



OTHER INTEREST GROUPS

AIDS Interest Group

Meeting time and place: Varies
Contact: Fulvia Veronese
Phone: 496-3677
E-mail: <veronesef@od.nih.gov>
ListServ: subscribe to AIDSINTG-L

Apoptosis Interest Group

Meeting time: 1st Monday, 4:00 pm
Meeting place: Building 30, Conference Room 117
Contact 1: Colin Duckett
Phone: 594-1127
E-mail: <ducketc@helix.nih.gov>
Contact 2: Yves Pommier
Phone: 496-5944
E-mail: <yp4x@nih.gov>

Behavioral and Social Sciences Interest Group

Meeting time: Varies, in the fall and spring
Meeting place: See NIH Calendar of Events
Contact 1: Jaylan Turkkan
Phone: 443-1263
E-mail: <jaylan@nih.gov>
Contact 2: Ronald Abeles
Phone: 496-7859

BSSR Methodology and Measurement Interest Group

Meeting time: First or second Tuesday, 8:30 am
Meeting place: Building 45, Room 3AS10
Contact: Jared Jobe
Phone: 496-3137
E-mail: <Jared_Jobe@nih.gov>

Bioethics Interest Group

Meeting time: 1st Monday (except 2nd Monday, September; usually does not meet during summer), 3:00 pm
Meeting place: Natcher, Room D, or Building 31, conference room 7; check yellow sheet or web site
Contact: Miriam Kelty
Phone: 496-9322
E-mail: <mk46u@nih.gov>

Biophysics Interest Group

Meeting time and place: Varies (often Building 10, Bunim Room)
Contact: Peter Basser
Phone: 435-1949
E-mail: <pjbasser@helix.nih.gov>

Birth Defects and Teratology Interest Group

Meeting time: Quarterly seminars
Meeting place: Videoconference between Bethesda and Research Triangle Park, N.C.
Contact 1: Megan Adamson
Phone: 443-4354
E-mail: <madamson@willco.niaaa.nih.gov>

Breast Cancer Think Tank

Meeting time and place: Varies
Contact 1: JoAnne Zujewski
Phone: 402-0985
E-mail: <zujewski@nih.gov>
Contact 2: Patricia Steeg
Phone: 496-9753

Calcium Interest Group

Meeting time: Usually Tuesday, 3:00 pm
Meeting place: Building 49, Room 1A50
Contact 1: Arthur Sherman
Phone: 496-4325
E-mail: <asherman@nih.gov>



Contact 2: Indu Ambudkar
Phone: 496-1478
ListServ: Subscribe to CALCIUM-L

Cancer CAM Research Interest Group

Meeting time and place: Varies
Contact: Jeffrey White
Phone: 435-7980
E-mail: <jeffreyw@mail.nih.gov>

Chemistry Interest Group

Meeting time: (Almost) Monthly seminars
Meeting place: Varies
Contact 1: John Schwab
Phone: 594-5560
E-mail: <schwabj@nigms.nih.gov>
Contact 2: Kenneth Kirk
Phone: 496-2619

Chromatin and Chromosomes Interest Group

Meeting time: Every other Thursday (except summer), 11:00 am
Meeting place: Building 32T, Conf. Room
Contact: David Clark
Phone: 496-6966
E-mail: <djclark@helix.nih.gov>

Clinical Immunology Interest Group

Meeting time: Monthly, last Wednesday, noon
Meeting place: Building 10, Room 9S235
Contact: Oral Alpan
Phone: 402-3447
E-mail: <oalpan@nih.gov>

Clinical Pharmacology Interest Group

Meeting time: 2-3 times a year in conjunction with special lectures in the NIH Principles of Clinical Pharmacology course, 6:30-7:30 pm
Meeting place: Building 10, Lipsett
Contact: Donna Shields
Phone: 435-6618
E-mail: <dshields@mail.cc.nih.gov>

Cognitive Neuroscience Consortium

Meeting time: Every two months, last Wednesday, 4:15 pm
Meeting place: Building 31, Room 6C10 (starts 8/30/00; extramural program directors' forum: last Friday every 3rd month, 4:15 pm, NSC Building, Conf. Rm. 2120, starts 7/28/00)
Contact: Emmeline Edwards
Phone: 496-9964
E-mail: <ee48r@nih.gov>

Cornea Interest Group

Meeting time: 1st Monday, 8:30 am
Meeting place: Building 6, Room 409
Contact 1: Joram Piatigorsky
Phone: 496-9467
E-mail: <joramp@intra.nei.nih.gov>
Contact 2: Janine Davis
E-mail: <davisj@intra.nei.nih.gov>

Cultural and Qualitative Research Interest Group

Meeting time: 1st Wednesday, 9:00 am
Meeting place: Neuroscience Center, B1/B2
Contact 1: Suzanne Heurtin-Roberts
Phone: 443-0639
E-mail: <sheurtin@willco.niaaa.nih.gov>
Contact 2: Wendy Smith
Phone: 443-8771

Cytokine Interest Group

Meeting time: Quarterly symposia
Meeting place: Varies
Contact 1: Rachel Caspi
Phone: 435-4555
E-mail: <rcaspi@helix.nih.gov>
Contact 2: Howard Young
Phone: 1-301-846-5700
E-mail: <youngh@mail.ncifcrf.gov>

Developmental Biology Interest Group

Meeting time and place: Varies
Contact 1: Tom Sargent
Phone: 496-0369
E-mail: <tsargent@nih.gov>
Contact 2: Peggy Zelenka
Phone: 496-7490
E-mail: <zelenkap@intra.nei.nih.gov>

DNA Repair Interest Group

Meeting time: 3rd Tuesday, 12:30 pm
Meeting/Videoconference: Natcher, Room H; GRC (Baltimore), Room 1E03; FCRDC, Building 549, Conf. Rm. A; NIEHS (Research Triangle Park, NC) Building 101, Room B200; SUNY, Stony Brook; University of Texas, MD Anderson Cancer Center, Smithville, TX; Lawrence Livermore (CA) National Laboratory; University of Michigan, Ann Arbor; University of Kentucky, Lexington
Contact 1: Kenneth Kraemer
Phone: 496-9033
E-mail: <kraemerk@nih.gov>
Contact 2: Vilhelm Bohr
E-mail: <vbohr@nih.gov>

Domestic Violence Research Interest Group

Meeting time and place: To be announced
Contact: John Umhau
Phone: 496-7515
E-mail: <umhau@nih.gov>

Drosophila Interest Group

Meeting time: 3rd Tuesday, 1:15 pm
Meeting place: Building 6B, Room 4B429
Contact 1: Sue Haynes
Phone: 295-9791
E-mail: <shaynes@usuhs.mil>
Contact 2: Jim Kennison
E-mail: <kennisoj@exchange.nih.gov>

Drug Discovery Interest Group

Meeting time: Usually one Thursday a month, 3:00 pm
Meeting place: Building 37, Room 5A21
Contact: John Weinstein
Phone: 496-9571
E-mail: <weinstein@dpax2.ncifcrf.gov>

Economics Interest Group

Meeting time and place: Varies
Contact 1: James A. Schuttinga
Phone: 496-2229
E-mail: <js41z@nih.gov>
Contact 2: Agnes Rupp
E-mail: <ar24f@nih.gov>

Endocrinology Interest Group

Meeting time and place: Varies
Contact 1: George Chrousos
Phone: 496-5800
E-mail: <George_Chrousos@nih.gov>
Contact 2: Phil Gold
Phone: 496-1945

Epidemiology and Clinical Trials Interest Group

Meeting time and place: Varies (subscribe to ListServ for notices)
Contact 1: Martina Vogel-Taylor
Phone: 496-6614
E-mail: <martinav@nih.gov>
Contact 2: Bill Harlan
Phone: 496-1508
ListServ: subscribe to Epidem-L at listserv@list.nih.gov

Epilepsy Interest Group

Meeting time: Wednesdays, 3:00 pm
Meeting place: Building 10, Room 5S235
Contact: Timothy Dunn
Phone: 402-2978
E-mail: <dunnt@ninds.nih.gov>

Fluorescence Interest Group

Meeting time: 2nd and 4th Friday, 4:00 pm
Meeting place: Building 10, usually Room 5N264
Contact: Jay Knutson
Phone: 496-2557
E-mail: <jaysan@helix.nih.gov>
Contact 2: Dan Sackett
Phone: 594-0358
E-mail: <sackettd@mail.nih.gov>

INTERINSTITUTE INTEREST GROUP DIRECTORY

Gene Therapy Interest Group

Meeting time: 2nd and 4th Thursday, 2:00 pm
 Meeting place: Building 10, Lipsett Auditorium
 Contact 1: Richard Morgan
 Phone: 402-1833
 E-mail: <rmorgan@nhgri.nih.gov>
 Contact 2: Fabio Candotti
 Phone: 402-1833

Genomics and Bioinformatics Interest Group

Meeting time: Usually one Thursday a month, 3:00 pm
 Meeting place: Building 37, Room 5A21
 Contact: John Weinstein
 Phone: 496-9571
 E-mail: <weinstein@dtpx2.ncifcrf.gov>

Glycobiology Interest Group

Meeting time and place: Varies
 Contact: Diana Blithe
 Phone: 435-6990
 E-mail: <blithed@nih.gov>
 ListServ: Subscribe to GLYCO-L@LIST.NIH.GOV

GTP Binding Proteins Interest Group

Meeting time: Irregular
 Meeting place: FAES Social & Academic Center
 Contact: R. Victor Rebois
 Phone: 496-2007
 E-mail: <rebois@box-r.nih.gov>



Hard Tissue Disorders Interest Group

Meeting time: Day varies, 9:30 am
 Meeting place: Building 30, Room 117
 Contact: Pamela Robey
 Phone: 496-4563
 E-mail: <probey@yoda.nidr.nih.gov>
 Contact 2: Michael Collins
 Phone: 496-4913

Head and Neck Cancer Interest Group

Meeting time: To be announced
 Meeting place: Building 30, Room 117
 Contact 1: Adrian Senderowicz
 Phone: 594-5270
 E-mail: <adrian.senderowicz@nih.gov>
 Contact 2: Wendy Weinberg
 Phone: 301-827-0709
 E-mail: <weinberg@cber.fda.gov>

History of Biomedical Research Interest Group

Meeting time: Second Tuesday, 3:30 pm
 Meeting place: Varies; check web site
 Contact 1: NIH History Office
 Phone: 496-6610
 Contact 2: Victoria Harden
 E-mail: <hardenv@od31tml.od.nih.gov>

Human Development Across the Lifespan Interest Group

Meeting time and place: By e-mail alert
 Contact: Kim Roberts
 Phone: 496-0420
 E-mail: <kim_roberts@nih.gov>

Image Processing Interest Group

Meeting time: 3rd Thursday, 11:00 am
 Meeting place: Building 10, Room B1N256
 Contact 1: Benes Trus
 Phone: 496-2250
 E-mail: <trus@helix.nih.gov>
 Contact 2: Matt McAuliffe
 Phone: 594-2432

Integrative Neuroscience Interest Group

Meeting time: Alternate Thursdays, 4:00 pm
 Meeting Place: Building 49, Room 1A51
 Contact: Betsy Murray
 Phone: 496-5625, X-227
 E-mail: <eam@ln.nimh.nih.gov>

In Vivo NMR Interest Group

Meeting time: Varies
 Meeting place: Building 10, Room B1N256
 Contact: Jeff Duyn
 Phone: 594-7305
 E-mail: <jhd@helix.nih.gov>

Java Interest Group

Meeting Time: 2nd Thursday, 4:00 pm
 Meeting place: Building 12B, second floor Conference Room
 Contact: Jai Evans
 Phone: 594-2900
 E-mail: <evansj@helix.nih.gov>

Knowledge Management Interest Group

Meeting time and place: to be determined
 Contact: Geoffrey Marsh
 Phone: 594-2423, ext. 213
 E-mail: <geoff@mail.nih.gov>

Lambda Lunch (Bacterial and Phage Genetics)

Meeting time: Each Thursday, 11:00 am
 Meeting place: Building 36, Room 1B13
 Contact: Susan Gottesman
 Phone: 496-3524

E-mail: <susang@helix.nih.gov>
 Anonymous FTP site: FTP.CU.NIH.-GOV
 directory "LAMBDA_LUNCH"

Light Microscopy Interest Group

Meeting time: Monthly, Tuesday, noon
 Meeting place: Building 10, Room 4B51
 Contact 1: James McNally
 Phone: 402-0209
 E-mail: <mcnally@exchange.nih.gov>
 Contact 2: Tilmann Brotz
 Phone: 435-6402

Lymphoma and Leukemia Interest Group

Meeting time: Varies
 Meeting place: Building 10, Room 12S235a
 Contact: Michael Bishop
 Phone: 435-2764
 E-mail: <mbishop@mail.nih.gov>
 ListServ: LLig-1

Mass Spectrometry Interest Group

Meeting time: 1st and 3rd Thursday, 11:00 am
 Meeting place: Building 10, Room 7C101
 Contact: Lewis Pannell
 Phone: 402-2196
 E-mail: <L_Pannell@nih.gov>

Microarray Users Group

Meeting time and place: Varies
 Contact: Katherine Peterson
 Phone: 496-3059
 E-mail: <katherine_peterson@nih.gov>

Microtubule Interest Group

Meeting time: Varies
 Meeting place: Building 10, Room 9S235 (Bunim Room)
 Contact: Dan Sackett
 Phone: 594-0358
 E-mail: <sackettd@mail.nih.gov>

Mitochondria Interest Group

Meeting time: 1st Monday, 3:00 pm
 Meeting/Videoconference: Natcher, Room H; NIEHS, Research Triangle Park, NC; GRC, Baltimore; University of California at Davis; University of Maryland, Baltimore
 Contact: Steve Zullo
 Phone: 435-3576
 E-mail: <zullo@helix.nih.gov>

Molecular Modeling Interest Group

Meeting time: See <http://mignet.nih.gov/MMIG>
 Meeting place: Building 12A, conf. rooms
 Contact: Peter Steinbach
 Phone: 496-1100
 E-mail: <steinbac@helix.nih.gov>

Motility Interest Group

Meeting time: 1st Monday, 4:00 p.m.
 Meeting place: Building 10, Bunim Room (9S235)
 Contact: Jim Sellers
 Phone: 496-6887

Mouse Club

Meeting time: 1st Tuesday, 4:00 pm
 Meeting place: Building 31, Room 2A52, or Building 6A, Room 405
 Contact: Heiner Westphal
 Phone: 402-0545
 E-mail: <hw@helix.nih.gov>

Mycobacterial Interest Group

Meeting time: Alternate Mondays, 10:30 am
 Meeting place: Building 29, Room 121, or Twinbrook II, 2nd-floor conference room
 Contact 1: Clifton Barry
 Phone: 435-7509
 E-mail: <clifton_barry@.nih.gov>
 Contact 2: Mike Brennan
 Phone: 496-9559

Nerve-Muscle Interest Group

Meeting time: Alternate Wednesdays, 9:00 am
 Meeting place: Building 36, Room 1B07
 Contact 1: Matt Daniels
 Phone: 496-2898
 E-mail: <mdaniels@codon.nih.gov>
 Contact 2: Zuhang Sheng
 Phone: 435-4596

Neural-Immune Interactions Interest Group

Meeting time: One Tuesday a month (except July and August), 4:00 pm
 Meeting place: Building 10, Room 11S235
 Contact: Craig C. Smith
 Phone: 496-4561
 E-mail: <ccs@codon.nih.gov>

Neurobiology Interest Group

Meeting time: alternate Fridays, 4:30 pm
 Meeting place: Cloisters, Rathskeller
 Contact 1: Chip Gerfen
 Phone: 496-4341
 E-mail: <gerfen@helix.nih.gov>
 ListServ: <http://intra.ninds.nih.gov/nig/>

Neuroinformatics Interest Group

Meeting time: 2nd Tuesday, 12:00 noon
 Meeting place: Building 49, Conference Room 1A/B.
 Contact 1: Rochelle Small
 Phone: 402-3464
 E-mail: <rochelle_small@nih.gov>
 Contact 2: Yuan Liu
 Phone: 496-3108

**PET Interest Group**

Meeting time: Each Friday, 2:00 pm
 Meeting place: Building 10, Room 1C520.
 Contact: Peter Herscovitch
 Phone: 402-4297
 E-mail: <herscovitch@nih.gov>

Phase-Tech Interest Group

Meeting time and place: Varies
 Contact 1: Steve Zullo
 Phone: 435-3576
 E-mail: <zullo@helix.nih.gov>
 Contact 2: Carl Merrill
 Phone: 435-3583

Pigment Cell Research Interest Group

Meeting time: 3rd Monday, 3:00 pm
 Meeting place: Building 49, first-floor Conf. Room
 Contact 1: Bill Pavan
 Phone: 496-7584
 E-mail: <bpavan@nhgri.nih.gov>
 Contact 2: Vincent Hearing
 Phone: 496-1564

Protein Trafficking Interest Group

Meeting time: 2nd Tuesday, 3:30 pm
 Meeting place: Building 10, Room 9S235
 Contact 1: Harris Bernstein
 Phone: 402-4770
 E-mail: <harris_bernstein@nih.gov>
 Contact 2: Peng Loh
 Phone: 496-3239

RNA Club

Meeting time: 1st Tuesday (except August), 4:00 pm
 Meeting place: Building 41, Room C509
 Contact 1: Carl Baker
 Phone: 496-2078
 E-mail: <ccb@nih.gov>
 Contact 2: Susan Haynes
 Phone: 301-295-9791
 E-mail: <shaynes@usuhs.mil>

Science Writing Interest Group

Meeting time and place: To be announced
 Contact 1: Edward McSweeney
 Phone: 402-8370
 E-mail: <emcsweeney@niaid.nih.gov>
 Contact 2: Alisa Machalek
 Phone: 496-7301

Signal Transduction Interest Group

Meeting time: Alternate Fridays, 4:30 pm
 Meeting place: 5 Research Court, Room 2A08
 Contact 1: John Northup
 Phone: 496-9167
 E-mail: <drjohn@codon.nih.gov>
 Contact 2: James Battey
 Phone: 402-0900

Synaptic and Developmental Plasticity Interest Group

Meeting time: Wednesday, 12:00 noon
 Meeting place: Building 49, Room 1A50
 Contact 1: Serena Dudek
 Phone: 402-4795
 E-mail: <dudek@helix.nih.gov>
 Contact 2: Bai Lu
 Phone: 435-2970

Therapeutic Oligonucleotides Interest Group

Meeting time: Last Thursday, 4:00 pm
 Meeting place: Building 10, Room 2C16
 Contact : Yoon Cho-Chung,
 Phone: 496-4020
 E-mail: <chochung@helix.nih.gov>

Transcription Factors Interest Group

Meeting time: 1st Thursday (except July-Sept.), 1:30 pm
 Meeting place: Building 49, Conf. Rm. B
 Contact 1: Stoney Simons
 Phone: 496-6796
 E-mail: <steroids@helix.nih.gov>
 Contact 2: Uli Siebenlist
 Phone 496-7662
 ListServ: subscribe to TFACTORS

Tumor Angiogenesis & Invasion Working Group

Meeting time and place: Posted at web site
 Contact 1: William Figg
 Phone: 402-3622
 E-mail: <wdfigg@helix.nih.gov>
 Contact 2: Steven Libutti
 Phone: 496-5049

Viral Hepatitis Interest Group

Meeting time: One Monday a month, 3:30 pm
 Meeting place: Building 10, 9S235 (Bunim)
 Contact: T. Jake Liang
 Phone: 496-1721
 E-mail: <jliang@nih.gov>

Virology Interest Group

Meeting time: Mini-symposia 1-2 times/year
 Meeting place: to be announced
 Contact 1: Klaus Strebel
 Phone: 496-3132
 E-mail: <kstrebel@nih.gov>
 Contact 2: John Patton
 E-mail: <jpatton@niaid.nih.gov>
 ListServ: Contact <CBuckler@nih.gov>

INTERINSTITUTE INTEREST GROUP DIRECTORY

Washington Area Yeast Club

Meeting time: 2nd Wednesday, 5:15 pm
 Meeting place: Building 6B, Room 4A05
 Contact 1: Reed Wickner
 Phone: 496-3452
 E-mail: <wickner@helix.nih.gov>
 Contact 2: Alan Hinnebusch
 Phone: 496-4480
 E-mail: <ahinnebusch@nih.gov>

Women's Reproductive Health Interest Group

Meeting time and place: Every four months at times decided by the group.
 Contact: Phyllis Leppert
 Phone: 496-6515
 E-mail: <LeppertP@nih.gov>

WorldWideWeb Interest Group

Meeting time: 2nd Tuesday, 2:30 pm
 Meeting place: Building 10, Lipsett Auditorium
 Contact 1: Sandy Desautels
 Phone: 402-6553
 E-mail: <sandy_desautels@nih.gov>
 Contact 2: Dale Graham
 Phone: 402-1805
 E-mail: <degraham@helix.nih.gov>

Xenopus/Zebrafish Interest Group

Meeting time: Last Monday (except summer), 3:30 pm
 Meeting place: Building 6B, Room 429
 Contact 1: Brant Weinstein
 Phone: 435-5760
 E-mail: <bw96w@nih.gov>
 Contact 2: Ajay Chitnis
 E-Mail: <chitnisa@mail.nih.gov>

X-ray Crystallography Interest Group

Meeting time: Quarterly, announced by e-mail, 2:00 pm
 Meeting place: Building 5, Room 127
 Contact: Xinhua Ji
 Phone: (301) 846-5035
 E-mail: <jix@ncicrf.gov>

Addenda

Considering starting a new Interest Group? Contact Celia Hooper (fax: 301-402-4303; e-mail:

<hooperc@nih.gov>.

Need to correct your group's listing? Contact CIT's web publishing group:

<publish@cit.nih.gov>.

FELCOM: An Intro

As its name implies, the NIH Fellows committee (FELCOM) was established to serve the NIH fellows community. It therefore draws its members from each NIH institute and from both basic and clinical science. FELCOM representatives are elected for a one-year term, act as liaisons between postdoctoral fellows and NIH administrative bodies, and serve as ad hoc members of several NIH-wide committees, including the CME committee and the Committee on Scientific Conduct and Ethics.

A major FELCOM program is the Fellows Award for Research Excellence (FARE). Held annually in May, this competition is based on abstracts submitted for blind peer review by study sections composed of two postdoctoral fellows and one senior scientist. The winners receive a \$1,000 travel award to attend and present their work at a scientific meeting, and they also present a poster to the NIH community in conjunction with a Wednesday Afternoon Lecture Series (WALS) event. FELCOM also sponsors up to three WALS lectures each year.

Ongoing events include the Survival Skills workshops, aimed at teaching fellows how to become independent investigators, and a series

on Scientific Careers for the Millennium. FELCOM also tackles such issues as visas, and it promotes the following teaching activities:

■ **Adventure in Science** shows children ages 8–11 the excitement of scientific discovery. Meets Saturdays October through March. Volunteers select their own material. Contact Edward Max (<max@cber.fda.gov>).

■ **NIH Resident Teacher Program** enlists fellows who want to teach science in Montgomery County public schools at the middle and high school levels. Offers a chance to earn state teacher certification. Contact Sandra Shmookler (phone: 301-279-3432; fax: 279-3428; or e-mail: <Shmookler@fc.mcps.k12.md.us>).

■ **FAES** seeks teachers for its college-level evening courses—from guest lecturers to course developers; monetary compensation is possible. Contact Constance Noguchi at 301-496-1163 or see website:

<<http://www.faes.org>>.

Current FELCOM chairs are Patricia Van Bergen and James Gulley; meetings (first Thursday each month at 4, Building 1) are open. For more info:

<<ftp://helix.nih.gov/FELCOM/index.html>>.

—Elizabeth McNeil, NCI
 Suzanne Dashiell, NINDS

An Apple For Excellence

The NIH Fellows Committee is requesting nominations for the 2000 Distinguished Clinical Teacher Award. Each year an NIH senior clinical investigator who has demonstrated excellence in clinical training involving direct patient care is publicly honored. A brief supporting statement should accompany nominations. Please fax or e-mail your nomination letter to:

Distinguished Clinical Teacher Award

Attention: Deborah Cohen, NIH
 Office of Education

Fax: 301-402-8975;

e-mail:

<fellows@box-f.nih.gov>.

The **deadline** for receipt of nomination letters is **August 30, 2000.** ■

George, I think
 your results
 are biased.



What structural biologists call an
 induced fit.

RECENTLY TENURED

C. Norman Coleman received his M.D. from Yale University in New Haven, Conn., and trained in internal medicine at UCSF, medical oncology at NCI, and radiation oncology at Stanford (Calif.) University, where he served on the faculty for seven years. Before returning to NIH as director of the Radiation Oncology Sciences Program (ROSP), he was the Fuller-ACS Professor and Chairman of the Joint Center for Radiation Therapy at Harvard Medical School from 1985 to 1999.

My foremost objective at NIH is to develop the ROSP, which is a program that combines expertise among the intra- and extramural branches relating to radiation oncology—specifically, the Radiation Oncology Branch, Radiation Biology Branch, and Radiation Research Program.

The field of radiation oncology deals with all tumor types, and the efficacy of radiation therapy depends on the response of both the tumor and the normal tissue within the radiation field. To exploit new advances in imaging, technology, and molecular biology, the ROSP program will collaborate extensively with other cancer specialists within NIH, surrounding universities, the region, and other research centers.

Radiation delivery requires definition of the target and normal tissue and the assessment of their response to treatment. To that end, our technical research and development work includes anatomical and functional imaging, real-time imaging (ultrasound or MRI) during radiation to assure beam targeting, optical sensors for dose calculation, and dose-calculation modeling of radiation-tissue interaction at the cellular and subcellular level.

We are now planning a Technology Development and Assessment Center within the Radiation Oncology Branch. One goal of the new center will be to develop implantable micro- and nanosensors to measure biological processes before, during, and after a range of treatments and to assess rapidly the molecular and cellular response to treatment by tumor and normal tissue.

The biological aim of the ROSP is to understand the tissue, cellular, and molecular response of tumors to radiation alone and in combination with radiation-modifying agents. We also want to develop improved therapeutics based on tumor genotype and phenotype. The

programs that we are establishing toward these goals include a microarray facility at the NCI's Division of Clinical Sciences Advanced Technology Center in Rockville, Md., and an in vitro and in vivo facility at FCRDC to study and assess radiation-drug interactions.

My primary personal research interest is in developing new therapeutics based on molecular targeting. Although radiation is typically described as an average dose to a tissue, at the end of its path in

tissue, the energy is delivered in dense packets. Furthermore, radiation can be focused to tissue via external beam, implanted sources, and systemically administered isotopes. Thus, our conceptual model is that radiation is "focused biology" that can perturb a wide range of cellular targets. This perturbation can be exploited with molecu-

lar therapeutics. Moreover, because many of the newly developed cancer treatments—such as antiangiogenesis agents or signal transduction modifiers—are cytostatic and not cytotoxic, radiation may be essential to make the agents effective in killing tumor cells.

My research interest over the past decade has been targeting the tumor microenvironment, including tumor hypoxia, which is present in about half the tumors studied. This not only leads to radiation resistance, but the microenvironmental stress and hypoxia itself can alter cellular phenotype, for example, the induction of HIF-1-responsive genes. Microenvironmental perturbation within tumors, such as an abnormal redox state, may alter protein structure and function.

James Mitchell's group in the Radiation Biology Branch is advancing this work by developing techniques to image hypoxia in real-time that would help guide therapeutics. My own laboratory interest has turned to the role of the cyclooxygenase inhibitors as enhancers of tumor cell killing. We have demonstrated that the nonspecific nonsteroidal anti-inflammatory drug ibuprofen is an effective radiation sensitizer in vitro and in vivo. We are investigating possible mechanism(s) for this effect, including perturbation of arachidonic acid metabolism, inhibition of NF κ B, which is constitutively active in a number of cancers,

and possibly through the action of PPAR (peroxisome proliferator-activated receptors) family.

ROSP is now recruiting basic molecular biology researchers, physicists, and engineers for the biomolecular sensor program and clinicians interested in translational research. We welcome inquiries and look forward to collaborations with colleagues at NIH.



Fran Pollner

Norman Coleman

Barney Graham received his M.D. from the University of Kansas, Kansas City, in 1979 and completed clinical training and a fellowship in infectious diseases at Vanderbilt University in Nashville, Tenn., in 1986; in 1991, he completed his Ph.D. in microbiology and immunology at Vanderbilt, where he is currently a professor of medicine in the Division of Infectious Diseases and an associate professor of microbiology and immunology. He will join the NIH Vaccine Research Center as the director of clinical trials, commuting on a regular basis as soon as the building is ready and settling in next spring.*



Barney Graham

My primary research interests are viral pathogenesis and vaccine development. I have focused on two major areas of work, AIDS vaccine evaluation in clinical trials and pathogenesis of respiratory syncytial virus (RSV) in a murine model. My specific recent interest in this area is in the role of RhoA, a small GTPase, in RSV entry, morphogenesis, and pathogenesis. I am also interested in science

education and expanding research opportunities for African-Americans and other underrepresented minorities. In this regard, I am a member of the Development Committee for National Medical Fellowships, Inc., and a mentor in the Fellowship Program in Academic Medicine for Minority Students sponsored by Bristol-Myers Squibb.

Since 1987 I have been involved in the development of the AIDS Vaccine Evaluation Group, recently renamed the HIV Vaccine Clinical Trials Network (HVTN). This group has collectively conducted more than 40 Phase I and II clinical trials of candidate AIDS vaccines. I chaired the initial human studies evaluating recombinant Vaccinia virus vectors, including studies combining a live recombinant

* The September-October issue of The NIH Catalyst will include a story on new VRC recruits and programs. A ceremony to mark the official opening of the VRC is planned for October.

RECENTLY TENURED

virus with a subsequent subunit protein booster.

In addition, I chaired studies evaluating novel adjuvants for subunit envelope antigens, and multivalent peptide vaccines combining both B- and T-cell epitopes. I also chaired the studies evaluating subjects who developed breakthrough HIV-1 infection despite prior vaccination, and I served in leadership positions for all the major subcommittees in the HVTN. I am particularly interested in the use of cytokines, chemokines, and other natural immuno-modulators as vaccine adjuvants, and in the evaluation of vaccine approaches that combine immunogens, delivery vehicles, and routes of administration.

My laboratory focus is to define basic mechanisms of RSV pathogenesis and to apply this knowledge to vaccine development. RSV is an important cause of respiratory disease that has received high priority for vaccine development. Previous vaccine candidates have failed in clinical trials, and a formalin-inactivated whole virus (FI-RSV) preparation was associated with vaccine-enhanced illness.

After early studies characterizing a murine model of RSV infection and defining the role of T cells and antibody in primary RSV infection, we addressed the pathogenesis of the FI-RSV vaccine-enhanced disease. My laboratory demonstrated that priming with inactivated RSV induces a type 2 T-helper lymphocyte (Th2) response (dominant IL-4 expression), whereas priming with live RSV induces a Th1-like response (dominant IFN- γ expression) in mice following RSV challenge.

We have subsequently used the murine RSV model to evaluate new vaccine approaches and to investigate how immunization determines the composition of immune responses. Specific projects include defining the mechanisms by which: 1) the RSV G glycoprotein induces IL-5 and eosinophilia, 2) IL-4 modulates the cytolytic mechanism of CD8 $^{+}$ cytolytic T cells, 3) RSV-induced immune responses interact with allergic inflammation to cause airway hyperresponsiveness, 4) co-administered antigens influence RSV-induced immune responses and lung pathology, and 5) integrins mediate lymphocyte trafficking and activation during RSV infection. The studies specifically aim to answer questions about in vivo phenomena, taking advantage of a variety of knockout and transgenic mouse strains and assays designed

to avoid in vitro artifacts.

A recent discovery in my laboratory of a cellular ligand for the RSV F glycoprotein has led to new projects in the areas of RSV-induced membrane fusion and viral entry and the role of intracellular signaling pathways triggered by the RSV F interaction in virus morphogenesis, immunity, and disease.

Our belief is that understanding basic mechanisms of antiviral immunity and viral pathogenesis will lead to novel and more effective approaches to vaccine development. Both laboratory and clinical studies yield essential information that must be integrated to inform the process of vaccine development.

Michael Krause received his Ph.D. from the University of Colorado in 1986 and did postdoctoral work with the late Harold Weintraub at the Fred Hutchinson Cancer Research Center in Seattle. He joined the NIDDK Laboratory of Molecular Biology in 1993 and is now a senior investigator heading the Section on Developmental Biology.

I am interested in transcriptional regulation of cell fate during development. I use the nematode *Caenorhabditis elegans* as an experimental system.

C. elegans adults have only 959 somatic cells and develop from an essentially invariant cell lineage over the course of three days. The nearly complete genome sequence of *C. elegans* became available last year, revealing about 19,000 genes. Recent techniques, using traditional mutagens and/or molecular approaches, make it possible to quickly create loss-of-function phenotypes for most genes. The combination of relatively simple anatomy, defined cell lineage, complete genomic information, and powerful forward and reverse genetics makes this organism an ideal system in which to study the transcriptional regulation of cell fate.

My lab focuses primarily on the regulation of muscle cell fates in *C. elegans*, including the early events of mesodermal patterning that underlie the formation of the correct type, number, and position of muscle cells. Some of the muscle types in *C. elegans* can be correlated with muscle types found in mammals and many of the transcription factors involved in mammalian myogenesis

have homologs in *C. elegans*. The simple anatomy of *C. elegans* allows us to study the function of these transcription factors in a single cell, sometimes revealing functions obscured in more complex animal systems.

A landmark discovery in the field of myogenic cell fate was the identification of the protein MyoD. MyoD is a basic helix-loop-helix (bHLH)-type transcription factor restricted primarily to skeletal muscle cell precursors; MyoD is not present in cardiac or smooth muscle. MyoD activates transcription of multiple downstream genes to cause proliferating cells to exit from the cell cycle and initiate the skeletal muscle program of differentiation. MyoD is one of four highly related proteins that together make up a family of myogenic factors in mammals. The identification of MyoD validated the notion of "master" regulatory genes capable of initiating whole programs of differentiation and marked the beginning of an intense research effort on skeletal muscle differentiation.

I arrived at the NIH shortly after identifying the only *C. elegans* homolog of MyoD (CeMyoD) and having shown that the expression profile of CeMyoD was consistent with its playing a key role in myogenesis. In collaboration with Andy Fire's group at the Carnegie Institution of Washington in Baltimore, we used CeMyoD knockouts to show that skeletal muscle-like cells in the nematode (body wall muscle)

can be formed in the absence of CeMyoD activity. This observation is surprising, because mammalian tissue culture studies and mouse knockout experiments demonstrate that some members of the mammalian MyoD family are essential for skeletal myogenesis. Although CeMyoD is not essential for body wall muscle formation in *C. elegans*, it is required for these cells to function; homozygous CeMyoD-null animals cannot move normally and die shortly after the embryo hatches.

Through work in my lab at NIH, we have now shown that the CeMyoD finding is just one in a series of observations revealing both conservation and divergence in the function of several highly conserved, muscle-associated transcription factors in *C. elegans*. Through further dissection of the functions of these factors we have found that embryonic and postembryonic periods of myo-



Fran Pollner

Michael Krause

genesis in *C. elegans* use different regulatory pathways. These results have implications beyond the nematode and help to explain some of the dramatic differences between *C. elegans* and other organisms in the function of these evolutionarily conserved factors.

More recently we have turned our attention to another bHLH transcription factor, Twist, which acts early in the myogenic pathway. We have identified mutants in Twist that reveal that it is required for patterning a subset of the muscles in *C. elegans*. Twist also functions in a subset of mesodermal tissues during mammalian development, and Twist mutations in humans result in Saethre-Chotzen syndrome, which affects craniofacial development. We are interested in studying CeTwist in more detail to identify interacting factors and downstream target genes.

Together with other labs, we have begun to identify the transcriptional hierarchy regulating postembryonic muscle cell fates in *C. elegans*. Future work is aimed at adding additional detail to the regulatory network of genes and defining pathways functioning in other muscle cell types. It should be possible to describe in complete molecular detail how each muscle cell of *C. elegans* arises, beginning with fertilization of the egg. By defining developmental paradigms, this will be an important milestone, not only for myogenesis but for developmental biology in general.

Chris McBain received his Ph.D. from the University of Cambridge, England, in 1988 and did postdoctoral work at the University of North Carolina and Duke University, both at Chapel Hill, before joining the Laboratory of Cellular and Molecular Neurophysiology of NICHD in 1993. He is now a senior investigator heading the Section on Cellular and Synaptic Physiology.

It is becoming clear that to begin to understand the coordinated activity of large ensembles of neurons, we must first understand the nature of transmission between individual pre- and postsynaptic elements within a circuit and each and every neural element involved. My interests are in elucidating the precise nature of excitatory and inhibitory synaptic transmission between specific identified neural populations within the hippocampal and cortical formations.

For the hippocampal neuronal network, the net flow of information is

strongly modulated by the action of the local-circuit GABAergic inhibitory interneurons, whose cell bodies are distributed throughout all layers of the hippocampus and comprise about 10 to 15 percent of the total neuronal population. The importance of these inhibitory neurons is underscored by the number of animal models of epilepsy that result from manipulation or loss of these inhibitory pathways.

My research has found that, rather than act as GABAergic counterparts of glutamatergic excitable cells, interneurons possess both intrinsic and extrinsic properties that set them apart from principal cells of the cortical formation. This divergent cell population can be distinguished by the molecular identity of receptors and channels they express, by their mechanisms of short- and long-term synaptic plasticity, and by signal transduction mechanisms associated with both ligand- and voltage-gated receptors.

Work in my lab has focused primarily on three areas of research. The first is the nature of synaptic plasticity regulating hippocampal inhibitory interneuron excitability. We found that, in contrast to principal cells, interneurons do not possess conventional forms of N-methyl-D-aspartate (NMDA)-receptor postsynaptic long-term plasticity, but are influenced indirectly by a "passively propagated" form of plasticity occurring within a polysynaptic pathway.

In addition, we demonstrated cell-specific expression of presynaptic forms of plasticity at synapses formed by the axons of dentate gyrus granule cells, the so-called mossy fibers. Target specificity of presynaptic plasticity results from the segregated expression of cAMP-dependent signaling cascades. This signaling pathway is targeted to presynaptic axons associated with principal cells but is absent at the same synapses made onto inhibitory interneurons. Expression of glutamate receptor proteins is similarly segregated on the postsynaptic side of interneuron synapses. Within a single cell the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-preferring class of glutamate receptors, which permit the entry of calcium ions, are expressed exclusively at mossy fiber synapses, while Ca-impermeable AMPA receptors are associated with inputs arising from the CA3 pyramidal neurons.



Fran Pollner

Chris McBain

Such receptor and axonal targeting act to increase the computational power of both individual neurons and their associated network. Future experiments will investigate the mechanisms responsible for receptor targeting to specific synapses.

The second area of interest in our lab emerged as we realized that to fully under-

stand the role played by an individual cell within a neural network it was also important to elucidate the intrinsic properties of each cell type. These intrinsic properties largely dictate how the cell integrates and responds to the thousands of synaptic signals arriving on its dendritic processes. To this end we investigated the role, the developmental expression, and subcellular localization of a variety of potassium channel subtypes (namely, Kv2.1, Kv4.2, Kv3.1, and Kv3.2) expressed in interneuron subpopulations.

We found that the temporal and spatial overlap of each K channel subunit dictates the firing pattern and integrative properties of each interneuron subpopulation. Interestingly, a picture is emerging that members of the Kv3 family are downstream targets for neurotransmitters and modulators (for example, histamine) that activate protein kinase A (PKA) cascades. PKA phosphorylation of Kv3 channels reduces currents through these channels, consequently setting the upper limit of fast spiking within inhibitory interneurons, which, in turn, pace high-frequency oscillations within the hippocampal network.

Our third area of interest emerged as a natural extension of our research into hippocampal function. Collaborative studies with Tony Wynshaw-Boris (NHGRI, now UCSF) investigated an animal model of the neurological disorder type I lissencephaly. Type I lissencephaly is a neuronal migration disorder that affects 1 in 40,000 children annually in the United States. Seizures are universal in people with type I lissencephaly, but precisely how a deficiency of the LIS1 protein disrupts normal brain development and precipitates seizures is not known.

By combining molecular, immunohistochemistry, and electrophysiological approaches, we demonstrated severe neuronal dysplasia and heterotopia throughout the hippocampal and cortical formations of both human lissencephalic hippocampus and mice contain-

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ing a deletion of the *Lis1* gene. Mechanisms of synaptic transmission were severely disrupted, revealing hyperexcitability of the hippocampus and a predisposition for electrographic seizure activity. These data are the first to pinpoint the neuronal basis of seizures associated with lissencephaly within the hippocampus. We will continue to use clinically relevant animal models to investigate the intrinsic properties, synaptic transmission, and receptor targeting in defined neuronal networks.

Toru Miki received his Ph.D. from Kyoto University, Japan, in 1979. He taught at Yamaguchi University School of Medicine, Ube, before joining the Laboratory of Cellular and Molecular Biology, NCI, in 1985. He is now chief of the Molecular Tumor Biology Section in the Basic Research Laboratory, NCI.

My research interests are in molecular mechanisms that convert normal cells to cancerous cells. To explore this field, I have developed an efficient expression cloning system and used it to isolate cDNAs that can convert normal fibroblasts into morphologically transformed cells. In an earlier study, we introduced an epithelial cell expression library into NIH3T3 cells and identified three morphologically distinct foci of transformed cells, from which we rescued three transforming cDNA clones designated *ECT* (epithelial cell transforming genes).

We soon identified *ECT1* as a receptor of keratinocyte growth factor (KGF). KGF is related to fibroblast growth factors (FGFs), but specifically targets epithelial cells. Several research groups were in the process of isolating FGF receptors at that time, and structural comparison of KGF receptor and FGF receptor-2 (FGFR2) revealed a difference only in a small region of the ligand-binding domain, suggesting that these receptors are encoded by alternative transcripts of a single gene. This finding established that ligand binding specificity can be determined by alternative splicing.

We also isolated a constitutively activated FGFR2 from rat osteosarcoma cells. Acquisition of a new sequence, designated FRAG1, at the COOH-terminus of FGFR2 played a major role in the activation by overriding the negative regulatory effect of the normal ligand-binding domain. Finally, we found that FGFR2

isoforms with an acidic amino acid stretch were heavily modified with glycosaminoglycans. The modified receptor exhibits sustained activation of MAP kinase and stimulation of DNA synthesis. This modification event is also regulated by alternative splicing, because the modification site is encoded by an alternative exon.

In contrast to *ECT1*, which exhibits structural homology to several protein kinases, *ECT2* initially lacked structural information. However, our continued attempts to isolate novel transforming genes from different cell types, as well as accumulation of new protein sequences in databases, led us to new members of this group of oncogenes, which share structural motifs of the guanine nucleotide exchange factors for the Rho family GTPases. While these oncogenes, *ECT2*, *OST*, *TIM*, *NET1*, and *NTS*, share common motifs, they also display distinct features. *OST* comprises multiple isoforms, catalyzes guanine nucleotide exchange on RhoA and Cdc42, and associates with Rac1 in its GTP-bound form. *OST* also regulates the JNK/SAPK MAP kinase pathway and induces actin reorganization in fibroblasts. *NET1* is one of the genes induced with oxidative stress. *NTS*, an exchange factor for Rac1, is a major nucleolar antigen expressed in proliferating, but not resting, cells.

Most of my recent interests are in the biological functions of *ECT2*. Besides the Rho exchange factor homology domain, *ECT2* also contains domains related to several molecules involved in cell-cycle checkpoint control and repair. We have recently found that *ECT2* is a critical molecule regulating cell division. *ECT2* functions as a guanine nucleotide exchange factor for Rho GTPases and is phosphorylated specifically in G2 and M phases. Interestingly, this phosphorylation is required for the exchange activity of *ECT2*. Unlike other exchange factors, *ECT2* localizes in the nucleus in interphase, but spreads to the entire cell after nuclear membrane breakdown. During cell division, *ECT2* localizes at the cleavage furrow and then the midbody. Inhibition of *ECT2* activity in cultured cells either by microinjection of anti-*ECT2* antibody or expression of dominant-negative isoforms strongly inhibits cytoki-

nesis. *ECT2* also localizes in spindle microtubules during mitosis.

We have recently cloned *Xenopus ECT2* and are studying its function in mitosis using a *Xenopus* in vitro cell-cycle control system. We are also increasing our attempts to clarify the role of Rho exchange factors in cell-cycle control.

Bob Seder received his M.D. from Tufts University in Boston in 1986 and completed a residency in internal medicine at Cornell University-New York Hospital. He came to NIH in 1989 as a postdoctoral fellow in the Laboratory of Immunology, NIAID, and is currently chief of the Clinical Immunology Section in the Laboratory of Clinical Investigation, NIAID.

Cellular immunity plays an important role in protecting hosts from a variety of infectious pathogens. These include fungal (such as *Histoplasma capsulatum*),

parasitic (*Leishmania major*, *Toxoplasma gondii*), mycobacterial (*Mycobacterium tuberculosis*, *M. avium* complex), and bacterial (*Listeria monocytogenes*) pathogens. Over the past 15 years, the increase in opportunistic infections in individuals infected with HIV has underscored the importance of the cellular immune response in

mediating protection against some of these pathogens. Despite a greater understanding of the factors regulating immune responses against these pathogens, patients often died from these infections due to an inadequate immune response. The worldwide pandemic of *M. tuberculosis* infection further attests to the need for understanding protective primary and memory cellular immune responses, which could lead to effective vaccines.

Protective immunity to many intracellular pathogens requires a complex sequence of events involving cells of the innate and acquired immune response. While innate immune response does provide some protection, acquired cellular immune response appears essential for sterilizing immunity and maintaining effective memory responses. Cytokines, such as IL-12, operate as a critical link between innate and acquired immunity. Their effect on the immune response overall and specifically on CD4+ T-cell differentiation has been the major focus of my career and current laboratory.

The importance of CD4+ T cells in regulating immune responses was highlighted by the seminal observation that



Bob Seder



Toru Miki

CD4⁺ T-cell clones could be segregated into specific subsets—Th1 and Th2—based on their pattern of cytokine production. This distinction and its importance in vivo provided a framework to examine the factors involved in the generation of these subsets. In my postdoctoral lab, we showed that cytokines such as IL-12 and IL-4 were potent regulators of Th1 and Th2 differentiation, respectively. Based on these observations, my current laboratory is using a variety of experimental infectious disease models to further understand the role of cytokines in immune regulation in vivo. To this end, we have studied three human pathogens (*H. capsulatum*, *M. tuberculosis*, *L. major*) in vivo. We also use these models to study cytokines as the basis for new therapies and vaccines.

Our recent work applies our understanding of how cytokines alter specific immune responses to a daunting challenge—the development of vaccines against intracellular infection. The great success of all existing vaccines depends on long-lived humoral immune response via antibodies. These responses to bacteria and viruses are readily achieved by many different vaccine formulations. By contrast, there are no uniformly effective vaccines for infections such as tuberculosis, malaria, and HIV, which now account for a majority of the deaths worldwide from infection. For all of these infections, a cellular immune response mediated by CD4⁺ and/or CD8⁺ T cells is required for protective immunity.

We have used the mouse model of *Leishmania major* infection, which requires Th1 responses, to study how long-term cellular immunity can be induced in vivo. Our results so far have shown that plasmid DNA vaccination encoding a specific leishmanial antigen induces long-lived protective responses in mice. This work has led us to explore whether this approach can work in nonhuman primates. If successful, we will follow up these studies in humans to determine safety and efficacy. We hope that this model will also help guide a rational approach for vaccination against *M. tuberculosis*, which requires a similar type of immune response.

Wei Yang received her Ph.D. from Columbia University in New York in 1991 and did postdoctoral work at Yale University in New Haven, Conn. In 1995, she joined the Laboratory of Molecular Biology of NIDDK, where she is now a senior investigator.

I have been interested in protein-DNA interactions for quite some time. Trained to be a biochemist and X-ray crystallographer in graduate school, I became fascinated by DNA recombination during my postdoc period at Yale University. At that time, I determined the crystal structure of a site-specific recombinase, *gd-resolve*, complexed with a 34-bp substrate DNA. Since joining NIH, my group has widened the research target from DNA recombination to mismatch repair and has taken a combinatorial approach, including X-ray crystallography, biochemistry, and mutagenesis, to study mechanisms of both processes.

DNA repair is an essential biological process in all living organisms. Mistakes in base pairing occur during DNA replication and are routinely repaired. MutS, MutL, and MutH are necessary and sufficient to initiate methyl-dependent mismatch repair in *Escherichia coli*. MutS possesses an ATPase activity and initiates repair by recognizing DNA containing mispaired or unpaired nucleotides. After binding to a mismatch, MutS recruits MutL to mediate the activation of MutH endonuclease, which cleaves the newly synthesized strand 5' to a transiently unmodified d(GATC) sequence. Both MutS and MutL also play essential roles in the subsequent removal and resynthesis of the daughter strand. The mismatch repair proteins MutS and MutL are conserved from prokaryotes to humans, and defective human homologues, for example, MSH, PMS, and MLH1 proteins, have been directly implicated in hereditary nonpolyposis colon cancers (HNPCC) and other familial and sporadic cancers.

During the past four and a half years, we have determined the crystal structures of MutH, a conserved 40-kD fragment of MutL (LN40), and LN40 in complex with an ATP analog and with the product ADP. Most recently, in collaboration with Peggy Hsieh's group (GBB, NIDDK), we have determined crystal structures of *Thermus aquaticus* MutS alone, its complex with DNA, and a ternary complex of MutS, DNA, and ADPMg²⁺. Based on these structures, we identified the active site residues of MutH and the MutS ATPase, and we confirmed the functional importance of these residues by mutagenesis. The crystal structures of MutS and its complex with DNA revealed the mode of mismatch recognition, which is based on the instability of heteroduplex DNA at



Fran Pollner

Wei Yang

mispaired or unpaired bases. We also uncovered an ATPase activity intrinsic to MutL that previous investigators had concluded did not exist.

Using hydrodynamic methods and crystallography, we have shown that binding of ATP triggers a structural transformation of MutL. Finally,

we have developed an in vitro assay for initiation of mismatch repair. Combining our structural, mutagenesis, and biochemical results, we have proposed a proof-reading mechanism of mismatch recognition by MutS—similar to that found in protein synthesis and DNA replication, but the first example identified in DNA repair processes. Our studies of mismatch repair proteins also have shed light on defects of mutations in HNPCC kindreds.

The other project my research group has been focused on is V(D)J DNA recombination, which is a site-specific event essential for the assembly of the immunoglobulin (Ig) and T-cell receptor (TCR) genes in the vertebrate immune system. The Ig and TCR genes are encoded in separate V, D, and J segments. Each segment has multiple copies with slight variations in sequence. By combinatorial means of joining V, D, and J segments into Ig and TCR genes and modifying the junctions between segments in somatic cells, immune systems are able to make millions of different Igs and TCRs from a limited set of coding sequences.

The V(D)J recombination is initiated by the combined action of two lymphoid-specific proteins, RAG1 and RAG2, which introduce double-strand breaks at the borders of the V, D, and J segments. The second stage of V(D)J recombination is to process and rejoin the cleaved coding ends of V, D, and J segments to form the mature Ig and TCR genes. Several proteins involved in the general repair of DNA double-strand breaks, including the catalytic subunit of DNA-dependent protein kinase, Ku protein, XRCC4 and ligase IV, are required for the second stage of V(D)J recombination. Mistakes at any stage of the V(D)J can cause cancers, growth and developmental defects, and premature death in humans. We are studying almost all of the involved proteins and in collaboration with Martin Gellert's group (LMB, NIDDK) have succeeded in determining the crystal structure of XRCC4. We are continuing to unravel the structure and function of macromolecular complexes involved in DNA repair and recombination. ■

CALL FOR CATALYTIC REACTIONS

In this issue, we are asking for your reactions in four areas: retirement, NIH programs for graduate students, Interest Group participation, and Hot Methods

Send your responses on these topics or your comments on other intramural research concerns to us via e-mail:

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In Future Issues...

- VRC Update
- PRAT Fellows:
■ Yesterday and Now
- Addiction Research

1) This is a repeat question: We are planning an issue that concentrates on retirement and how retired scientists conduct their lives after they leave the NIH campus, and we still want to hear your anecdotes about other scientists, plans of your own, retirement philosophy—really almost anything on this potentially thorny transition.

2) With a new director of graduate program partnerships, Mary DeLong, NIH will be looking for ways to improve and expand programs for graduate students. What would you recommend?

3) What role does your participation in other groups have in your life as an NIH scientist?

4) Are there any "Hot Methods" out there?

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2W23, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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